

Claims

1. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an organic solvent and isolation of an amorphous product.
2. The process according to claim 1, wherein an organic solvent is selected from the group consisting of lower C1-C4 alkanols.
3. The process according to claims 1 and 2, wherein an organic solvent is methanol.
4. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises:
  - a) dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an organic solvent,
  - b) concentrating the solution,
  - c) adding water,
  - d) precipitating the amorphous product,
  - e) optionally isolating the precipitated product to obtain amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester.

5. The process according to claim 4, wherein an organic solvent is selected from the group of lower C1-C4 alkanols.
6. The process according to claim 4, wherein an organic solvent is methanol.
7. The process according to claim 4, wherein the concentration of the solution is performed at reduced pressure to a point where the solution is clear.
8. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent and isolation of an amorphous product.
9. The process according to claim 8, wherein an inert organic solvent is selected from the group consisting of lower alkanols, chlorinated lower alkanes, ketones, aromatic hydrocarbons, cyclic ethers and nitriles.
10. The process according to claims 8 and 9, wherein an inert organic solvent is selected from the group consisting of methanol, chloroform, methylene chloride, acetone, benzene, toluene, tetrahydrofuran and acetonitrile.
11. The process according to claim 8 wherein the process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, comprises:

- a) dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent,
  - b) evaporation of the inert organic solvent,
  - c) isolation of the amorphous product.
12. The process according to claim 11, wherein the dissolving of crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent is performed at about room temperature or under heating up to about 60 °C.
13. The process according to claim 11, wherein an inert organic solvent is selected from the group consisting of lower alkanols, chlorinated lower alkanes, ketones, aromatic hydrocarbons, cyclic ethers and nitriles.
14. The process according to claims 11 and 13, wherein an inert organic solvent is selected from the group consisting of methanol, chloroform, methylene chloride, acetone, benzene, toluene, tetrahydrofuran and acetonitrile.
15. The process according to anyone of claims 8 and 11 wherein the isolation of the amorphous product comprises evaporating the inert organic solvent at room or increased temperature and at normal or reduced pressure.
16. (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an solid amorphous form.

17. (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an solid amorphous form with HPLC purity higher than 85%.
18. (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an solid amorphous form with HPLC purity higher than 95%.
19. (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an solid amorphous form with HPLC purity higher than 99%.
20. (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an solid amorphous form having an X-ray powder diffraction pattern substantially as shown in Figure 1.
21. (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an solid amorphous form having a DSC thermogram substantially as shown in Figure 2.
22. A process for the production of atorvastatin calcium comprising the steps of:

- a) dissolving the (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in the organic solvent,
- b) isolating amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester and
- c) using amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in the synthesis of atorvastatin.

23. Use of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an amorphous form in the production of atorvastatin.

24. The use of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester according to claim 22 wherein atorvastatin is in the form of a calcium salt.